2. BCDH Synopsis

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Clinical Study Report Synopsis: Study H9B-MC-BCDH

Title of Study: Phase 2, Dose-Ranging Study of Multiple Subcutaneous Doses of LY2127399, an Anti-BAFF Human Antibody, in Patients with Active Rheumatoid Arthritis Despite Ongoing Methotrexate Therapy

Number of Investigators: This multicenter study included 51 principal investigators.

Study Centers: This study was conducted at 51 study centers in 12 countries.

Publications Based on the Study: None at this time.

Length of Study: Date of first patient first visit: 18 November 2008
Date of last patient last visit: 27 December 2010

Phase of Development: 2

Objectives: The primary objective was to test the hypothesis that the ACR50 response after 24 weeks for the smallest dose that achieved at least 95% of the maximal efficacy (ED_{95}) of LY2127399 was significantly greater than for placebo, when study drug was administered subcutaneously (SC) every 4 weeks (Q4W) in patients with active rheumatoid arthritis (RA) despite ongoing methotrexate (MTX) therapy.

The secondary objectives were the following:

- To estimate the maximum response to LY2127399, the ED_{95}, and the smallest dose achieving this maximum response of ACR20 and ACR50 at 24 weeks.
- To determine whether there was a minimally effective dose (MED; the smallest dose with at least 25% absolute efficacy difference from placebo in ACR50 and in ACR20) and to estimate that dose.
- To evaluate the LY2127399 dose-ACR50 response and the dose-ACR20 response relationships at 24 weeks relative to placebo.
- To characterize relationships between LY2127399 dose, exposure, and response of selected pharmacodynamic (PD) endpoints including individual components of the ACR Core Set, ACR rates (20, 50, 70, and ACR-N), change in Disease Activity Score based on a 28 joint count (DAS28), and European League Against Rheumatism Responder index based on 28 joint count (EULAR28).
- To evaluate LY2127399 safety and tolerability compared to placebo.
- To evaluate PD of selected peripheral B cell subsets following administration of LY2127399 as compared to placebo.
- To explore the potential associations between selected biomarkers (baseline and response to study treatment) and selected disease activity measures.
- To further characterize LY2127399 pharmacokinetics (PK) in RA patients on MTX therapy.
- To evaluate the potential effect of LY2127399 compared to placebo on additional patient-reported outcomes as measured by the:
    - Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
    - Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

Study Design:
This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, outpatient study. Patients had active RA despite ongoing MTX therapy. Patients exposed to any tumor necrosis factor (TNF)α inhibitor for 3 or more months and having an inadequate efficacy response (as assessed by the investigator) were excluded. Patients had to be on a stable dose of MTX. This study used a Bayesian adaptive design.
After a burn-in period of 5 patients randomized per treatment arm, patients were adaptively randomized to placebo or 1 of 6 LY2127399 doses (1-, 3-, 10-, 30-, 60-, or 120 mg) administered SC Q4W. Patients received a total of 6 injections at 0, 4, 8, 12, 16, and 20 weeks. Patients completing the study were required to participate in at least 14 visits to the study site.
The primary visits included 2 screening visits (Visit 1 and Visit 1A) and 12 study day visits (at Week 0/Day 0, Day 1 [or 2 or 3], and Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, and 44). (Note: Patients who enrolled in the long-term extension study [BCDI] were not required to complete visits in the present study after Week 24.)
Safety was evaluated at all study visits. RA disease activity assessments were conducted from Weeks 1 through 44. Additionally, telephone visits were scheduled at 36 and 40 weeks to inquire about the patient's general health status and the progression of their RA, to determine whether any adverse events (AEs) had occurred, and to ask about any medication(s) the patient had taken since their last visit/call.
The study baseline was considered to be predose at Visit 2 (Week 0). Additional visits beyond 44 weeks could have been scheduled if needed to assess patient safety, including monitoring of B cell numbers.

Number of Patients: Planned: The minimum sample size was approximately 75 and the maximum was approximately 150. Initially, there were 5 patients randomized to each of the 7 treatment groups in equal proportion (1:1:1:1:1:1:1). After 35 patients were enrolled, subsequent patients were adaptively randomized to placebo or LY2127399 in a 1:4 ratio (20% to placebo and 80% to LY2127399 doses).
Randomized and Treated (at least 1 dose): The numbers of patients assigned to the placebo group and the LY2127399 doses of 1 mg, 3 mg, 10 mg, 30 mg, 60 mg, and 120 mg groups were 36, 30, 20, 15, 18, 13, and 26.
Completed (placebo or LY2127399 1 mg, 3 mg, 10 mg, 30 mg, 60 mg, and 120 mg) were 34, 26, 17, 15, 16, 13, and 21.

Diagnosis and Main Criteria for Inclusion: Ambulatory male or female patients between the ages of 18 and 75 years, inclusive, were enrolled in the study. Patients had a diagnosis of RA according to the American Rheumatism Association (ARA) 1987 Revised Criteria for the Classification of RA and at least 5 swollen and at least 5 tender joints based on the 28 joint count specified. Patients had been regularly using MTX for at least 16 weeks, and at a stable dose between 10 and 25 mg/wk, inclusive, for at least 8 weeks prior to baseline. Patients had a history of, or current, positive rheumatoid factor (RF) test. Patients were in ACR functional class I, II, or III, and had a screening C-reactive protein (CRP) of at least 1.2 times upper limit of normal (ULN).

Study Drug, Dose, and Mode of Administration: LY2127399 was administered as 2 x 1.0 mL SC injections of LY2127399 (for all doses) in the abdomen, thigh, or upper arm Q4W. There were 6 dose levels of LY2127399: 1, 3, 10, 30, 60, and 120 mg. Lots: [redacted], [redacted], and [redacted].

Reference Therapy, Dose, and Mode of Administration: Placebo (0.9% Sodium Chloride Injection) was administered as 2 x 1.0 mL SC injections of placebo or LY2127399 (for all doses) in the abdomen, thigh, or upper arm Q4W.

Duration of Treatment: The total duration of treatment was 24 weeks, i.e. 6 administrations of study drug.

Variables:
Efficacy: The primary efficacy variable was ACR50 response. Secondary efficacy variables included ACR20 response, ACR70 response, ACR-N, and ACR core set (tender joint count [28/68], swollen joint count [28/66], patient's assessment of joint pain, patient's assessment of disease activity, physician's assessment of disease activity, HAQ-DI, CRP, DAS28, and EULAR28 response). Additional patient-reported outcomes variables included duration of morning stiffness, FACIT Fatigue score, and SF-36 domain scales, physical health component summary (PCS) and mental health component summary (MCS) scores.
Safety: AEs, clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs).

Pharmacokinetic: A two-compartment open model was used in PK modeling, with both constant clearance (CL) and saturable clearance (CLSAT) terms as well as Michaelis-Menten constant (C50) to capture the nonlinearity of LY2127399 PK. Other PK parameters estimated were central volume (V1), peripheral volume (V2), distribution clearance (Q), and SC route specific parameters (i.e. first-order absorption rate constant from a depot [Ka] and absolute bioavailability [F]).

Pharmacodynamic**:** Cluster of determination (CD)20+ B cell counts, CD19+ cell counts, CD19+ B cell subsets (mature naïve [CD19+, CD27-, IgD+], immature/transitional [CD19+, IgD-, CD27-], memory [CD19+, IgD-, CD27+], and nonswitched memory [$CD19^{+}$, IgD+, CD27+]), T cells (CD3+, CD4+, and CD8+), natural killer cells (NK; CD16+ and CD56+), disease-related biomarkers (rheumatoid factor [RF], CRP, anti-cyclic citrullinated peptide antibody [anti-CCP], and erythrocyte sedimentation rate [ESR]), and serum immunoglobulins.

Evaluation Methods: Enrollment and randomization were planned to end when the maximum of approximately 150 randomized patients was reached, or the pre-specified stopping rule for futility had been met. Continuous variables were summarized using descriptive statistics and were analyzed using parametric or non-parametric tests as applicable based on the distribution of the variable. Discrete variables analyzed as 2-sided tests were analyzed using Chi-square tests; if assumptions of the Chi-square test were violated, then Fisher's Exact test was used. Key safety and efficacy data from the electronic case report form (eCRF) as well as any laboratory data (including bioanalytical and immunogenicity data) were listed by patient.

Efficacy: The primary efficacy variable was the ACR50 Responder Index (based on 28 joints) at Week 24 (last observation carried forward [LOCF]), where patients who discontinued from the study prior to Week 24 were imputed as non-responders. The primary null hypothesis was that there was no dose-response relationship in ACR50 responder rates at Week 24 (LOCF). The 1-sided alternative hypothesis was that there was an ACR50 dose-response relationship (higher doses had higher response rates for a linear trend test; or convex curvature for the quadratic test if the linear test was not significant) at Week 24 (LOCF).

The dose-response relationship was tested with a preliminary joint test of linear and quadratic dose-response prior to pairwise comparisons with placebo (i.e. the logistic regression model was of the form of dependent variable [ACR50 at Week 24 (LOCF)] = dose + $dose^2$).

With the exception of 0.1 level of significance (α) for primary analysis, analyses of key efficacy endpoints (ACR20, ACR50, ACR70, ACR-N, DAS28, EULAR28) were performed at the 0.05 level of significance (α) using 1-sided tests. The 1-sided alternative was that the LY2127399 treatment group would have superior efficacy to the placebo group during the post-injection study period. All other analyses were performed at the 0.05 level of significance (α) using 2-sided tests.

Safety: All safety data were descriptively summarized by treatment groups.

Bioanalytical and Pharmacokinetic/Pharmacodynamic: A two-compartment open model was used in PK modeling, with both CL and saturable clearance CLSAT terms as well as Michaelis-Menten constant (C50) to capture the nonlinearity of LY2127399 PK. For pharmacodynamic (PD) assessments, the visit values and change from baseline values were summarized using similar methods as described for the continuous secondary efficacy variables. An analysis of variance (ANOVA) with treatment as the fixed factor was performed to compare each LY2127399 dose group vs. placebo at each visit and at endpoint for the PD biomarkers

Summary

The Safety population included all randomized patients who received any amount of blinded study drug (LY2127399 or placebo, according to the treatment the patient actually received). This population consisted of 158 patients (36 patients in the placebo group and 122 patients in the all LY2127399 patients group) and was identical with the Intent-to-treat (ITT) population. Overall, 46 (29.1%) patients did not enroll in consecutive study H9B-MC-BCDI. This included 8 (22.4%) patients in the placebo group and 38 (31.1%) patients in the all LY2127399 group.

The mean age of the ITT population was 52 years and the mean age ranged from 44.4 years to 54.6 years across treatment groups. Overall, 63.9% of patients were Caucasian, 27.8% were Hispanic, and 6.3% were East Asian. The mean body mass index for the ITT population was 27.44 kg/m^2. Demographic and baseline parameters (tender and swollen joint counts, physician's global assessment of disease activity, patient's global assessment of disease activity, patient's global assessment of joint pain, HAQ-DI, CRP, RF and ESR) were comparable between treatment groups.

Efficacy

The primary efficacy endpoint was met as a significant dose-response relationship ($p = 0.059$, with a pre-specified type I error rate of 0.1) was detected based on ACR50 response rate at Week 24 (LOCF) using a predefined linear quadratic logistic regression model. Based on the Q4W dosing frequency used in this study, the estimated ED95 dose, 119 mg (close to the tested 120 mg dose), provided a statistically significant higher fitted response rate than placebo in ACR50 (37.0% vs. 18.1%, $p = 0.042$) based on the model's predicted response rates. For the PP population, a similar ED95 dose of 119.2 mg was estimated. The efficacy evaluation showed that the LY2127399 120 mg dose was an effective dose with a statistically significant higher response rate than placebo for model based data, but not for the observed data. In other measures of efficacy, the 120 mg group demonstrated significantly better efficacy than placebo in ACR20 observed response rate, ACR-N, DAS28 change from baseline, EULAR28 (good + moderate) responses, FACIT Fatigue, MCS score of the SF-36 and HAQ-DI scores. No clinically significant trends were observed for tender and swollen joints, joint pain, disease assessments, morning stiffness and CRP.

Pharmacokinetic

The PK of LY2127399 administered as SC injection were adequately described by a 2-compartment model with linear as well as nonlinear clearance. Body weight had a statistically significant effect on the PK of LY2127399, however, the effect does not warrant dose adjustment based on body weight. Age, gender, ethnic origin, baseline BAFF and creatinine clearance had no statistically significant effect on the PK of LY2127399.

Pharmacodynamic

All LY2127399 dose groups showed a similar pattern with an initial increase of mean CD20+ B cell counts at Week 1 and a subsequent decrease back to baseline level or even below from Week 4 on. Although mean decreases in mean CD20+ B cell counts were observed in all LY2127399 groups at Week 24, no direct association between strength of dose and magnitude of decrease was apparent. On the other hand, the differences to placebo in comparison to the all LY2127399 patient groups were statistically significant at Week 4, 16 and 24. After Week 24, except in the LY2127399 1 mg group, there were continued mean decreases of the absolute CD20+ B cell counts in all LY2127399 groups indicating a prolonged effect of LY2127399 on absolute CD20+ B cell counts. At Week 44, 18% of the evaluable patients did not meet the B-cell recovery criteria and returned for additional B-cell follow-up. Three of 5 patients recovered by Week 60, however, 2 were still below the lower limit of normal for CD20+ B cells at Week 72 (date of last sampling); both patients had received the 120 mg dose. Of the CD19+ cells, only the subset of mean mature naïve cell counts showed a pattern similar to the CD20+ cells with an initial increase at Week 1 and subsequent decrease to baseline or even below at Week 4. Mean immunoglobulin levels tended to be lower than baseline in all treatment groups over the course of the study. No clear relationship to treatment was indicated by changes from baseline in mean T cell counts, NK cell counts, RF levels, and anti-CCP levels over the course of the study. Mean ESR tended to decrease from baseline across treatment groups over the course of the study.

Safety

The incidence of serious AEs and AEs that led to discontinuation was low. The overall TEAE profile was within expectations for the study population, with worsening of RA being the most frequently observed TEAE overall. Injection site reactions (pain, irritation, erythema, pruritis) were experienced by 11 (9.0%) patients who received LY2127399 and were not observed in the placebo group. In 6 patients who experienced injection site pain at one investigational site, possible reasons for the multiple reports of injection site pain confined to the particular site were thoroughly investigated, but no cause was evident.

The occurrence of infections was higher in the all LY2127399 group in comparison with the placebo group, but the incidence of infection did not increase with higher doses of LY2127399.

No clinically important differences among treatment groups were apparent in the results of clinical laboratory data, vital signs, and ECG analyses. The overall incidence of treatment-emergent persistent immunogenicity for all LY2127399-treated patients was low (1.6%) and the anti-drug antibodies were not neutralizing. The development of immunogenicity was not associated with reductions in PK parameters, efficacy, or TEAEs and there was no indication of a relationship to dose. Two LY2127399-treated patients reported infectious TEAEs near the time of their B cell count nadir. The frequency of treatment-emergent infectious events in patients with a low B cell count postbaseline during the treatment period (2/8 or 25%) is not greater than the frequency of infectious events reported for the combined LY2127399 dose group (30.3%). Based on these data, an increased risk of infection (serious or non-serious) was not associated with a decrease in total B cell count to <43 cells/µL.

After Week 24, one death occurred, but this was deemed not related to the study medication by the investigator. Otherwise, no notable safety observations were made after Week 24.
LY2127399 was well-tolerated at each dose level investigated in this study. The safety profile of the LY2127399 120 mg was similar to the other dose groups.

Conclusions

The primary efficacy endpoint was met as a significant dose-response relationship ($p = 0.059$, with a pre-specified type I error rate of 0.1) was detected based on ACR50 response rate at Week 24 (LOCF) using a predefined linear quadratic logistic regression model. The efficacy evaluation showed that the LY2127399 120 mg dose was an effective dose with a statistically significant higher response rate than placebo for model based data, but not for the observed data. The estimated ED95 doses for ACR50 (119 mg) and ACR20 (118.5 mg) were essentially the same as the 120 mg dose tested in this study and provided a statistically significant higher fitted response rate than placebo. LY2127399 was well-tolerated at each dose level investigated in this study.